M-l – (1) Scientific Abstract

Age-Related Macular Degeneration (AMD) is, together with Diabetic Retinopathy, the most common cause of vision loss among adults in the US and other developed countries. In the US, at least 1.7 million people have impaired vision due to AMD. Every year, more than 165,000 people contract AMD and 16,000 go blind from it,[1] predominantly from a rapidly progressing form of the disease called "wet" AMD. Wet AMD is characterized by serious or hemorrhagic detachment of the retinal pigment epithelium and choroidal neovascularization. The macula has the highest concentration of photoreceptors facilitating central vision and permitting high-resolution visual acuity. The damage caused by the leakage and fibrovascular scarring in wet AMD leads to profound loss of central vision and severe loss of visual acuity (usually 20/200 or worse). People with wet AMD have several limitations, including inability to read, inability to recognize faces or drive, and the disease often leads to blindness. The onset of severe visual changes in wet AMD can occur suddenly. More than 400,000 Americans are currently affected by this form of the disease,[2] and the incidence is rising rapidly with the aging of the population. Therefore, the serious consequences of this disease along with the limited treatment options and their effectiveness make this a very good candidate for a gene transfer treatment approach.

The investigational agent, Ad_{GV}PEDF.11D, is an E1-, partial E3-, E4- deleted replication deficient, adenovirus serotype 5, gene transfer vector. The transgene in this vector is the cDNA for human pigment epithelium-derived factor (PEDF). PEDF is one of the most potent known antiangiogenic proteins found in humans. While Ad_{GV}PEDF.11D is able to transduce many somatic cell types, the natural barrier to other tissues created by the retina limits the ability of Ad_{GV}PEDF.11D to affect tissues other than in the eye. Intravitreal administration of Ad_{GV}PEDF.11D provides a convenient means of delivering PEDF to the relevant cells within the eye likely to result in a more prolonged duration of effect versus administration of the PEDF protein alone.

In three murine disease models (the laser-induced choroidal neovascularization model, the VEGF transgenic model, and the retinopathy of prematurity model) significant inhibition of neovascularization (up to 85%) was demonstrated with doses of Ad_{GV}PEDF vectors ranging from 1×10^8 to 1×10^9 pu. In toxicology studies performed in Cynomolgus monkeys, a dose-related inflammatory response was observed. A dose of 1×10^8 pu caused no adverse effects, while the inflammatory response observed at 1×10^9 pu was minimal and fully reversible. The observed inflammatory response at doses of $1 \times 10^{10}$and 5×10^{10} pu were increasingly severe.

The proposed clinical trial is an open-label, dose-escalation, phase I study to investigate the safety, tolerability and potential activity of intravitreal injection of Ad_{GV}PEDF.11D in patients with wet AMD. Ad_{GV}PEDF.11D will be injected once via intravitreal injection into the eye with the most advanced AMD based on visual acuity. Subjects will be age 50 or over and have severe wet AMD in at least one eye defined by a best-corrected vision of 20/200 or worse. The primary objectives of this investigation are: (1) to assess the safety, tolerability and feasibility of intravitreal injection of AdgvPEDF.1 1D in patients with severe, neovascular AMD, (2) to identify the maximum tolerated dose (MTD) of Ad_{GV}PEDF.11D, and (3) to get some indication of potential activity of Ad_{GV}PEDF.11D.

1. Department of Health and Human Services, National Eye Institute, Age-Related Macular Degeneration. Status of Research, Harold Varmus, March 1997.

2. Seddon JM. Epidemiology of age-related macular degeneration. In: *Retina*, 3rd Ed, Vol 2, pp. 1039-1050. Edited by SJ Ryan. Singapore: Mosby. 2001.